September 2003

To Advisory Committee Meeting Participants:

This document is the FDA's background package for the Ophthalmic Sub-Committee Meeting of the Dermatologic and Ophthalmologic Advisory Committee Meeting to be held on September 25, 2003, at the Gaithersburg Holiday Inn. The topic for discussion is the study design of trials in the treatment of myopia.

This package includes

   1. The Agency's briefing summary of clinical information, and

   2. Draft questions for discussion at the meeting.

Please direct any question concerning the meeting to Kimberly Littleton Topper, Advisors and Consultants Staff, at (301) 827-6755.

Ophthalmic Sub-Committee Meeting
Dermatologic and Ophthalmologic Advisory Committee
September 25, 2003

The Agency is seeking guidance from the Advisory Committee on the development of drug therapies to prevent or slow the progression of myopia.

An available therapy for myopia would carry important public health implications. The prevalence of myopia in the U.S. has been estimated at 20-50%[1]. It is not unrealistic to believe that parents will "demand" myopic prevention treatment for their child if they are under the impression that their child will benefit. This could result in unprecedented pediatric exposure to a chronically administered drug in a population of otherwise healthy children.

Several issues require consideration before a precedent for acceptable clinical trial criteria is set. Discussion toward developing an evidence-based approach is sought.

Natural History of Myopia

The long-term natural history of myopia (infancy through adulthood) has not been well studied. As a result, investigators have relied upon a variety of studies, frequently cross sectional, to draw inferences about the effect of myopia on ocular health. These studies have alternately suggested and refuted a wide variety of associations between myopia, various retinal diseases and glaucoma.

Even the generally accepted long-term natural history of *high myopia* is based only on observed anecdotal associations. Despite this absence of definitive trials, the ophthalmic community at large has accepted high myopia as an independent risk factor for a variety of retinal diseases (e.g., retinal tears, holes, detachments, retinopathy, CNV, etc.). Here, clinicians have brought to bear supportive evidence by buttressing anecdotally observed associations with speculations about the pathophysiologic mechanisms involved (e.g., retinal/choroidal stretching due to increased axial length). In the end, while associations might be hypothesis-generating, cause and effect can best be established by conducting large-scale longitudinal, prospective studies of adequate duration.

Factors influencing the development of Myopia

There are long standing debates over genetic factors versus environmental factors as being the primary cause of myopia. Neither appears able to explain all aspects of the development of myopia. Differences in ethnicity[2] have been noted to affect the frequency of myopia development in the United States. While it may be important to understand the cause to help select interventions, the failure to completely understand the cause is not necessarily a fatal flaw to studying an intervention.

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[1] Saw SM *et al*. Interventions to Retard Myopia Progression in Children. *Ophthalmology 2002*;109:415-427.
[2] Kleinstein RN *et al*. Refractive Error and Ethnicity in Children. *Arch Ophthalmol. 2003*;121:1141-1147.

Issues in Trial Design

The practical issues inherent to the study of myopia prevention make clinical trial design and implementation difficult. These issues include the long time span in which non lens-related refractive changes are observed (birth through age 30 years), requisite involvement of children, potential impact of genetic predisposition, educational level, light exposure, refractive correction, and behavioral patterns such as the frequency and duration of close work (reading). The long horizon from enrollment to clinically relevant events and a relatively low absolute event rate for anything other than a simple refractive error adds to the difficulty of designing a practical trial.

Therefore, the selected inclusion/exclusion criteria and the selected primary endpoint are critical to the proper selection of a study population with a high likelihood of maximizing clinical events.

Surrogate Endpoints

Clinical trials designed to study diseases with uncertain natural histories such as myopia often rely on surrogate markers to measure drug effect. Since no long-term studies have been conducted to assess the natural history of myopia, no surrogate marker has been validated as predictive of clinically relevant ocular disease. As with any proposed surrogate measure, a scientifically sound argument must be presented prior to acceptance by the Agency and should include any relevant preliminary data that might be supportive. Further, the Agency will ultimately require validation of any proposed surrogate measure.

Myopia as an Indication

It is unclear to the Agency at what level mild-to-moderate myopia, absent ocular pathology, is problematic requiring prevention. With the ability to accommodate intact, refractive errors ranging from +3 to -0.5 diopters provide generally excellent vision for all activities of daily living. After the ability to accommodate has been lost, refractive errors between -1 and -2 diopters still provide generally acceptable vision for most activities of daily living.

Measure/Definition of Myopia

It is unclear from existing studies whether the cause of myopia is relevant to a potential pathology. While there is general consensus among clinicians that an abnormal increase in axial length will contribute to retinal pathology, it is not clear whether myopia can cause retinal pathology in eyes of normal axial length. Until more is known, it seems important to use validated instruments to measure refractive error, axial length and corneal curvature.

Draft Questions being considered:

1) What is the minimum rate (amount and time) of refractive change that determines whether myopia is classified as:
   a) "Progressive"?
   b) "Stable"?
   c) "Regressing"?

2) Is there an accepted, evidence-based baseline characterization of patients who are at high risk of developing progressive myopia?

3) Which populations should be studied prior to approving a drug treatment for prevention or retarding myopia?
   a) Ages?
   b) Education levels?
   c) Ethic groups?
   d) Family history of myopia?
   e) Other defining characteristics?

4) What is the minimum, baseline level of myopia and/or a baseline set of associated factors that might justify a pharmacological intervention to arrest its progression?
   a) Minimum axial length?
   b) Minimum refractive error?
   c) Minimum corneal curvature?
   d) Period of time for changes to be observed?

5) What is the minimum amount of change that would justify a pharmacological intervention to arrest its progression?
   a) Minimum increase in axial length?
   b) Minimum rate of change in refractive error?
   c) Minimum change in corneal curvature?
   d) Period of time for changes to be observed?

6) What is the minimum amount of change that would is considered a pharmacological success in slowing progression?
   a) Minimum increase in axial length?
   b) Minimum rate of change in refractive error?
   c) Minimum change in corneal curvature?
   d) Period of time for changes to be observed?

7) "High" myopia has been attributed to a diminution in an individual's quality of life. How is "quality of life" most appropriately assessed in these clinical trials?

8) What is an ideal refractive error (or range of refractive errors)?

9) How much of a refractive change is considered an important change for an individual, who would otherwise have had the following refraction.
    a) Refractive error of 1 diopter or less?
    b) Refractive error of > 1 and ≤ 2 diopters?
    c) Refractive error of > 2 and ≤ 3 diopters?
    d) Refractive error of > 3 and ≤ 5 diopters?
    e) Refractive error of ≥ 5 and ≤ 7 diopters?
    f) Refractive error of >7 and < 12 diopters?
    g) Refractive error of ≥12 diopters?

10) Which method (or combination of methods) do you consider the most reliable and reproducible for the assessment for measuring myopia in children
    a) Automated refraction?
    b) Cycloplegic refraction?
    c) Ultrasound axial length measurement?
    d) Cycloplegic autorefracted spherical equivalent?
    e) Other?

11) How frequently should assessments be made?

12) Which are clinically relevant, acceptable endpoints of myopia-induced ocular disease?
    a) Development of a retinal tear?
    b) Development of a retinal detachment?
    c) Development of a retinal hole?
    d) Development of lattice degeneration?
    e) Development of glaucoma? How would glaucoma be defined?
    f) Development of retinopathy? How would retinopathy be defined?
    g) Other?

13) Trials should be of adequate duration to determine whether a therapy slows myopic progression, whether the effect is permanent as opposed to shifting the curve to the right, and whether there is a rebound effect after discontinuation. Assuming a best case scenario where the drug product halts the progression of myopia, what would be the minimum:
    a) Duration of treatment?
    b) Follow-up after treatment?

14) Refractive errors prior to age 7-9 years old may cause (or correct) amblyopia. Individuals ultimately developing high degrees of myopia frequently demonstrate refractive errors prior to ages 7-9 years.   Should children who are still at risk for developing amblyopia be studied or should studies be limited to older children?

15) Given the potential for wide use in a pediatric population, what level of adverse events should clinical trials in this area be designed to detected (1%? 0.5%? 0.1%, 0.05%, 0.01%, 0.001%, 0.0001%)? Would this answer change for a product which demonstrated a reduction in the frequency of retinal detachments?